REMARKS

The claims have been amended in light of the discussion at the interview. Claims 28-33 have been amended to reflect the fact that SEQ. ID. NO: 18 disclosed herein encodes a sufficient portion of a functional α_1 subunit of a T-type, low voltage activated calcium ion channel that an ordinarily skilled artisan, based on the information contained in SEQ. ID. NO: 18, could readily deduce a nucleotide sequence which would complete SEQ. ID. NO: 18 so as to encode a functional α_1 T-type low voltage activated calcium channel. Thus, the claims are directed to an expression system which is able to produce, in recombinant host cells, a functional α_1 subunit of a T-type calcium channel where the relevant encoding nucleotide sequence *comprises* a nucleotide sequence which encodes the amino acid sequence encoded by SEQ. ID. NO: 18 but which is supplemented by additional nucleotide sequence designed on the basis of SEQ. ID. NO: 18 which completes the necessary elements for functionality. This is verified and explained by the enclosed declaration of Dr. Terrance Snutch.

Briefly, the amino acid sequence encoded by SEQ. ID. NO: 18 is not the complete α_1 calcium ion channel; however, the amino acid sequence encoded by SEQ. ID. NO: 18 contains virtually all of the elements essential for functionality, and by virtue of the understanding of the structure of α_1 subunits in general, and the nature of the relationship of one portion to another, the deduced amino acid sequence encoded by SEQ. ID. NO: 18 provides the skilled artisan with the information to design an amino acid sequence which represents the small portion of the amino acid sequence lacking and required in order to obtain functionality.

As explained in Dr. Snutch's Declaration, voltage gated ion channels in general, and calcium ion channels in particular contain four homologous structural domains, assigned I, II, III and IV. All four are structurally and evolutionarily related to each other and each contains six transmembrane segments, including a transmembrane segment that acts as a voltage sensor, and a P-loop or Pore region that contains specific amino acid residues responsible for ion selectivity. It is thought that regions I, II, III and IV evolved from a single prototype, generally considered to

be region I; region II is thus highly homologous to region I and regions III and IV are highly homologous to regions I and II. The deduced amino acid sequence encoded by SEQ. ID. NO: 18 contains 1853 amino acids out of what is known to be an approximately 2300 amino acid protein (based on the characteristics of cloned channels), and, as the start codon is present at the 5′ end, it is clear from SEQ. ID. NO: 18 that all that is missing would be approximately 450 amino acid residues at the C-terminus. By analogy to known calcium ion channels, it can be determined that SEQ. ID. NO: 18 contains all of domains I, II and III and up to the first transmembrane segment of domain IV. Since, as noted above, domains I, II, III and IV are highly homologous, the information contained in the first three domains is sufficient to deduce a functional sequence for the fourth domain.* Thus, one of ordinary skill could readily construct a nucleotide sequence which encodes a functional channel with all four domains based on the amino acid sequence deduced from SEQ. ID. NO: 18.

Thus, the expression system claimed in claim 28 will encode a functional T-type calcium channel α_1 subunit by virtue of comprising a nucleotide sequence encoding the amino acid sequence of SEQ. ID. NO: 18 which can readily be supplemented by additional sequence deducible therefrom. Accordingly, the expression system produces a useful protein which can readily be used to screen for compounds which will be effective in treating a variety of conditions whose existence is known to result from abnormal functioning of T-type, low voltage activated calcium ion channel.

Claims 29-33 are essentially unchanged; claims 31-33 reflect recombinant host cells modified to contain the expression system and methods to produce and use the calcium ion channels described above.

The application makes clear that SEQ. ID. NO: 18 encodes a T-type, low voltage activated calcium channel and can be inserted into an expression system which is designed to

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* The sequence for the fourth domain need only be functional; it need not, of course, be identical to the native sequence in domain IV.

produce a functional α_1 subunit. As pointed out in the specification, T-type channels are low voltage activated channels which show transient activity at negative potentials and are sensitive to changes in resting potential. (Page 2, lines 24-26.) The α_1 subunit is active alone without α_2 δ and β subunits as set forth on page 3, lines 19-20. As pointed out further in the specification, it has been known for some time that the calcium channel α_1 subunits which are missing from the repertoire of cloned genes are those of the T-type channel. (See page 6, lines 4-6.) Thus, the "missing" α_1 subunit discovered here is associated with T-type activity, the only missing calcium ion channel from among encoding sequences already cloned.

Further, as pointed out in the specification, a number of indications are associated with improper function of T-type calcium channels. These are listed on page 9 of the specification, lines 7-12.

As explained at the interview, it was known at the time the application was filed that sequences encoding all of the known types of high voltage activated calcium channels were already available in the art. A number of other groups had attempted, using standard molecular biology techniques without success to obtain the genes for the T-type channels, which were known to malfunction in various conditions.

The present inventors were successful in obtaining a nucleotide sequence encoding a majority of the sequence of a T-type calcium channel α_1. The deduced amino acid sequence encodes almost all of the α_1 subunit beginning at the N-terminus and missing only approximately 400 amino acids (out of about 2300) from the C-terminus. Because the missing approximately 400 amino acids sequence is highly homologous to three homologous domains included in the retrieved sequence, the obtained nucleotide sequence provides all of the essential features of a functional α_1 subunit. As explained in the enclosed Declaration of Dr. Terrance Snutch, an analysis of the structure of the protein encoded by SEQ. ID. NO: 18 contains all the characteristic features which are required for calcium ion transport activity except for a repetition of sequences that are already present in SEQ. ID. NO: 18. The missing amino acids at the

C-terminus are deducible from the upstream regions. Thus, an expression system comprising SEQ. ID. NO: 18 can readily be constructed which produces a functional calcium ion channel as required by the claims.

Since SEQ. ID. NO: 18 and its deduced amino acid are described in the specification and characterized as encoding an α_1 subunit of a T-type low voltage activated calcium ion channel, and since SEQ. ID. NO: 18 can be used to construct a functional expression system based on the known characteristics of calcium ion channel α_1 subunits as described in Dr. Snutch's declaration, the limitations of claims 28-33 are clearly disclosed in the specification. No new matter has been added and entry of this amendment is respectfully requested.

New claim 34 is supported on page 15, lines 5-8 and by Example 1, specifically on page 16, lines 22-page 17, line 5. Thus, claim 34 does not constitute new matter either and entry of this amendment is also requested.

Formal Matters

The corrections to the drawings and description thereof have been made as requested; a new sequence listing has been submitted and the claims and specification have been modified to comport with the numbering in the Sequence Listing. It is believed the Sequence Listing is now in compliance with the rules. The sequences in the figures have been included in the sequence listing and the figures have been amended accordingly. It is believed that these formalities are now taken care of.

The Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office has objected to the term "medium hybridization stringency." Applicants have already, in the previous response, submitted a declaration indicating that one of ordinary skill in the art would understand what is meant by medium stringency conditions. These conditions represent a narrow range of conditions which is contrasted with high stringency and low stringency. These are conventional terms in the art. It is not clear from the rejection whether the

Office believes that the term "medium stringency" is not supported in the specification; however, this terminology is specifically supported in the specification at pages 14-15, bridging sentence. Indeed, these conditions are specified for the screening of cDNA libraries in particular.

With respect to the definiteness of these conditions, a very narrow range of conditions is understood to be meant by this terminology. These conditions are defined in the Declaration of Dr. Snutch previously submitted. Applicants have offered to arbitrarily chose a precise cutoff within these narrow conditions; however, they were informed at the interview that this would constitute new matter, although the conditions are themselves set forth in Dr. Snutch's declaration and are within the metes and bounds of medium stringency as understood by those of ordinary skill in the art. Under these circumstances, it is believed that the term "medium stringency" is sufficiently definite when taken in combination with the functional limitation that the sequence which hybridizes to the disclosed SEQ. ID. NO: 18 must successfully function in an expression system to produce a functional T-type calcium ion channel α_1 subunit which is activated at low voltage. Accordingly, this basis for rejection may be withdrawn.

The Office further objects that the name "α_1 subunit of the calcium ion channel" has not been defined in the claims and specification to allow the metes and bounds of the claims to be determined. Applicants do not understand this objection; perhaps it is remedied by the amended language of the claims which makes clear that the protein encoded by the claimed nucleotide sequence must *function* as an α_1 subunit of a T-type calcium ion channel which is activated at low voltage. This is clearly supported in the specification; it is explained on page 2, lines 24-26, that T-type channels transiently activate at negative potentials and are highly sensitive to changes in resting potential and are otherwise considered "low voltage activated." It is also made clear on page 5, line 15, that the α_1 subunits alone can form functional calcium channels. Assays for confirming the function of the encoded and expressed protein are described on page 18, beginning at line 14. It is respectfully submitted that the ordinarily skilled artisan understands the function of the α_1 subunit of a T-type calcium ion channel; understands that such α_1 subunit

can itself without association with other subunits function as a calcium ion channel and would understand how to confirm the function of a protein purported to be an α_1 subunit of a T-type, low voltage activated channel. Accordingly, the metes and bounds of the invention as set forth in this functional limitation would be well understood.

The references to SEQ. ID. NOS. have been conformed to the sequence listing submission enclosed herewith.

The Rejection Under 35 U.S.C. §§ 101/112

The Office asserts that the claimed subject matter has no well-established utility or asserted utility that is specific, substantial and credible. Nothing could be farther from the truth.

It is both well established and asserted in the specification that the calcium ion channel α_1 subunit produced by the claimed expression system and method is useful to screen for compounds which agonize or antagonize the T-type calcium ion channel and that antagonists of this channel are useful in treating specific conditions.

The association of abnormal T-type calcium channel activity with specific conditions is well known in the art. Enclosed herewith are a number of documents which verify this. Abnormal T-type activity is associated with a number of cardiac conditions including pacemaker activity (Hajiwara, *et al., J. Physiol.* (1988) 395:233-253; cardiac hypertrophy (Nuss, *et al., Circ. Res.* (1995) 73:777-782); and hypertension (Self, *et al., J. Vasc. Res.* (1994) 31:359-366). Abnormal T-type calcium function is also associated with neurological diseases wherein neuronal bursts are abnormally fired causing spastic convulsions (Huguenard, *Ann. Rev. Physiol.* (1996) 58:329-348) and thus associated with epilepsy (Tsakiridou, *et al., J. Neuro. Sci.* (1995) 15:3110-3117; Coulter, *et al., Brit. J. Pharmacol.* (1990) 100:800-806). Abnormal function of the T-type calcium ion channel is also associated with impaired fertility because of its effect on hormone secretion (Rossier, *et al., Endocrinology* (1966) 137:4817-4826; Arnoult, *et al., Proc. Natl. Acad. Sci. USA* (1996) 93:13004-13009). Copies of these documents are attached hereto. In addition, as recognized by the Office, the specification itself sets forth these conditions as

impacted by malfunction of T-type calcium ion channels on page 9, lines 7-12. Thus, there surely can be no argument that the α_1 subunits encoded by the nucleotide sequence set forth in claim 28 and its dependent claims or obtained by the method set forth in new claim 34 has a substantial, specific, and credible utility both established in the art and asserted in the specification.

It may be argued that there are several T-type calcium channel genes which encode different T-type channels and that therefore it would be necessary to identify specifically which of the T-type channels has been obtained in order to correlate the channel with the specific condition. It is true that the various T-type channels have differing tissue distributions and, depending on this tissue distribution, have effects with regard to a subset of the conditions set forth above. However, as outlined in the declaration of Dr. Snutch, because an antagonist for one T-type channel is an antagonist for all T-type channels, it does not matter in the context of a screening assay which T-type channel is used. The antagonist would be useful in the treatment of any of the foregoing conditions because all T-type channels would be impacted. It is not as if compounds which bind to the T-type channel associated with, for example, epilepsy would not also bind the T-type channel associated with cardiovascular disease. Thus, it is not required to associate a particular gene with a particular calcium channel within the T-type class.

At the interview, it was asserted that there is a *per se* rule that a nucleotide sequence is not useful unless it encodes a full-length protein as defined by an open reading frame begun with a start codon and ended with a termination codon and that there is a *per se* rule that methods to obtain a full-length sequence lack utility or do not comply with the written description requirement. Such putative *per se* rules clearly do not comport with the guidelines.

First, the guidelines themselves make clear that the guidelines do not "constitute substantive rule-making" and do not "have the force and effect of law," they are merely designed to assist Office personnel in analyzing the claimed subject matter.

More important, a reading of the guidelines themselves would not support the conclusion that the claimed subject matter has no substantial, specific and credible utility. Applicants have shown that not only is the utility well established, but it is also described in the specification.*

The Utility is Substantial

The use of a biological target for screening libraries of compounds as candidate pharmaceuticals is very well established. This is clearly a real-world utility since it is designed to lead to pharmaceuticals which are able to mitigate specifically defined serious physiological conditions. The mere fact that the calcium ion channel in this context is a "research tool" is not a disqualification. The reference to *Brenner v. Manson* as finding lack of utility where further research is required to obtain an end-point is not apposite. The further research required in *Brenner* was to find out something about the nature of the compound for which a process for preparation was claimed. In other words, in *Brenner*, the further research was to find out what the relevant compound was useful for. Here it is quite clear what the compound itself is useful for. Since it is linked to various undesirable physiological conditions, it is useful as a screening tool.

The Utility is Specific

At the interview, the question was raised as to specificity of this utility in the sense that all calcium ion channels are putatively not the same. The claims have been amended to focus on the particular T-type, low voltage activated channels which have clear nexus to specific disease

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* Applicants have been made aware of the proceeding in a perhaps analogous high-profile case which resulted in a settlement and thus is not reported as a court decision. As the Examiners may recall, the University of California brought suit against Genentech for infringing claims directed to recombinant materials for the production of human growth hormone. These claims were based on the University's having obtained a clone encoding all but the N-terminal amino acids of the known 191 amino acid sequence of human growth hormone. Genentech, in its defense, unsuccessfully asserted that the incomplete clone obtained by the University was not useful. This assertion was made despite the fact that Genentech actually used this clone and supplemented it with a synthetic nucleotide sequence encoding the missing 24 amino acids at the N-terminus. These facts are analogous to those here where sufficient clone sequence was obtained to permit others to construct the complete sequence.

states. This is unlike the case of cytokines cited by the Examiners at the interview where different cytokines have vastly different functions. All of the T-type calcium ion channels have the same connection to disease states. Thus, the utility is specific.

The Utility is Credible

As noted, the art recognizes the nexus between T-type calcium ion channels and various conditions. Documents in support of this are submitted herewith, as noted above. Further, this factual evidence of this recognition was presented by Dr. Snutch at the interview, and if the Office insists, can be included in a declaration. However, it is respectfully submitted that the Office has made no *prima facie* showing that the utility is not credible. As noted in the guidelines, such a *prima facie* showing *must* contain the following elements:

(1) an explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible;

(2) support for factual findings relied upon in reaching this conclusion; and

(3) an evaluation of all relevant evidence of record including utilities taught in the closest prior art.

It is respectfully submitted that none of these requirements has been met. The guidelines further state that:

> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such statement.

Again, no such evidence has been adduced.

The Partial Nucleotide Sequence of SEQ. ID. NO: 18 is Useful to Construct an Expression System for a Functional T-Type Calcium Channel

As set forth in the enclosed declaration by Dr. Terrance Snutch, the nucleotide sequence SEQ. ID. NO: 18 (1) encodes most of the α_1 subunit required for function and (2) provides

sufficient information so that the ordinarily skilled artisan can complete the sequence required for functionality. To the extent the rejection for lack of utility rests on the idea that insufficient structure exhibiting the claimed utility has been disclosed, the enclosed declaration should rebut this presumption.

Beyond an assertion that the utility requirement is not met, the Office goes on to assert that the claims are indefinite by virtue of a lack of meaningful structural limitation and no functional language, citing *Ex Parte Maizel*. It is not entirely clear what the statutory basis for this paragraph in the rejection is, (112 ¶ 1? 112 ¶ 2?, 101?) but it should be noted that the claims evaluated in *Maizel* and those here are quite different in their specificity. The claim in *Maizel* was directed to a recombinant DNA vector which encoded protein having a specified molecular weight and having an amino acid sequence which included what was evidently a portion of a full-length sequence, or a biologically functional equivalent thereof which had a specified function. The Board found the claim unpatentable under 35 U.S.C. § 112 as overbroad. The reason was that the underlined phrase above permitted the claim to cover DNA where there was no structural limitation whatsoever. The claim was directed to DNA encoding all proteins of any structure whatsoever which had a similar biological activity to the protein for which at least some structural features were described.

That is clearly not the case here. Claims 28-30 are limited to nucleotide sequences which encode proteins that have at least the amino acid sequence encoded by SEQ. ID. NO: 18 and those which are encoded by nucleotide sequences that hybridize under medium stringency conditions to nucleotide sequences encoding the protein having the specified amino acid sequence. Thus, specific structural limitations are imposed on the compositions within the scope of the claims, completely different from the situation in *Maizel* where absolutely no structural limitations were imposed. The definition of hybridization conditions as "medium" clearly sets metes and bounds on this structure since the nature of medium stringency conditions is well known in the art, and requires a degree of homology defined by these conditions. Applicants

enclose a copy of the *Maizel* decision confirming that it is the phrase "or a biologically functional equivalent thereof" which, having imposed absolutely no structural limitations, made the claim unpatentable.

In order to provide a complete response, applicants take note of the statement that the application gives no guidance "regarding what sequences would hybridize specifically to SEQ. ID. NOs: 18-19 and not other related sequences." It is not clear what is meant by this complaint. In order to hybridize to any specified sequence under specified conditions, it is well understood that a required degree of homology exists. It is unclear what is referred to by "not hybridizing to other related sequences." Of course, the claimed sequences will also hybridize to other related sequences. So what?

The Rejection Based on an Asserted Lack of Written Description is in Error

First, the guidelines themselves regarding written description make clear that this is a fact issue which must be resolved on a case-by-case basis. Therefore, it is inappropriate to apply a *per se* rule that in all cases a total open reading frame must be disclosed in order to meet this requirement. With respect to claims 28-33, a reading frame is set forth which translates into a portion (about 85%) of a complete reading frame sufficient to permit construction of the missing C-terminal portion, and so as to permit the construction of an expression system which will produce a functional calcium ion channel α_1 subunit. Thus, the proteins obtained from the expression of the nucleotide sequence as modified according to the knowledge of one of ordinary skill are useful and define compositions of matter whether or not this is the form in which the calcium ion receptor occurs in nature. Applicants are aware of no requirement that states that the encoded polypeptide must occur in nature.

The Office complains that SEQ. ID. NO: 18 is an "incomplete cDNA." It is an incomplete open reading frame, but this does not mean that it does not permit construction of an expression system for production of a functional protein. As to an appropriate reading frame, it will be noted that the deduced amino acid sequence permits diagnosis that the nucleotide

sequence of SEQ. ID. NO: 18 encodes approximately 85%, starting from the N-terminus, of a T-type calcium ion channel α_1 subunit and permits design of an amino acid sequence of the C-terminus which renders the protein containing the resulting amino acid sequence functional. It is this amino acid sequence that is functional, and therefore the nucleotide sequence that encodes it is functional as well.

The Office asserts that the claim encompasses polynucleotides which vary substantially in length and in nucleotide composition. This is not entirely true. The genus of nucleotide sequences is tightly defined by both functional and structural requirements.

The Office cites *Regents of the University of California v. Eli Lilly* in support of its position that the scope of the claim is inappropriate. A reading of the holding in this case, however, will verify that this is not an analogous case. Indeed, the position of the Office in this instance is out of sync with the guidelines proposed in response to the holding in *Lilly*. As stated in the guidelines, the applicant may show that an invention is complete by showing that the applicant had complete or partial structure, or had other physical or chemical properties or functional characteristics when they are coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. This is exactly what has been determined here. A high degree of homology to a nucleotide sequence encoding a sufficient portion of a functional protein to design the rest is required, along with a requirement that the protein have a specified function. This type of genus definition was not the subject of the holding in *Lilly*.

For example, one of the claims at issue in *Lilly* was directed to mammalian DNA encoding proinsulin *which was the reverse transcript of messenger RNA in a mammal.* Thus, the genus defined by the claim required the disclosure of the precise nucleotide sequence as it occurred in nature in each and every mammal. It did not take account of the degeneracy of the code, nor did it define a clear boundary of homologous molecules similar to rat proinsulin for which the nucleotide sequence was disclosed. The Court found that because it was unpredictable

what the reverse transcript of each and every mRNA would be, the applicant was not in possession of the invention as claimed.

This is in contrast to the present instance where there is no requirement that the sequences hybridizing under medium stringency conditions to SEQ. ID. NO: 18 or its complement be a precise reverse transcript of mRNA. The metes and bounds of the genus are set out by the hybridization conditions. The metes and bounds are also framed by requiring a functional activity. Applicants respectfully submit that there is no jurisprudence holding that this claim scope is unacceptable. The holding in *Lilly* is simply inapposite to the present claims.

The Office goes on to point out that the specification does not identify and describe the 5′ and 3′ regulatory regions and untranslated regions essential to the function of the claimed invention. These regions are not essential to the function of the invention. All the nucleotide sequence need do is encode the functional T-type α_1 subunit. The essential features of the invention are completely defined since the coding sequence for the functional protein is set forth in sufficient detail to permit the skilled artisan to make a functional protein. There is no genomic DNA required or claimed.

Finally, the Office states that "although the nucleotide [sic] of SEQ. ID. NOs: 18 and 19 may encode the α_1 subunit of calcium channel the disclosure no prior art disclose [sic] any polynucleotides that may bind the polynucleotide SEQ. ID. NOs: 18 and 19 and encode α_1 subunit of calcium channel." Applicants respectfully point out that variations in nucleotide sequences defined by hybridization conditions are standard methods for claiming a reasonable genus that includes a single disclosed polynucleotide sequence and do not unfairly extend the metes and bounds of the invention. One of ordinary skill in the art could readily, given enough time, write down all of the nucleotide sequences which would hybridize under these conditions to the disclosed sequences. The citation of *Fiers v. Revel* is inapposite as *Fiers v. Revel* concerned instances where no sequence information whatsoever was provided. The case is simply not analogous to that herein.

With respect to claim 34, it will be noted that the court in *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991) cert. denied, 502 U.S. 856 (1991) specifically provided that a nucleotide sequence although not disclosed in terms of A's, T's, C's and G's, could be claimed as a product of a process. That being the case, it is respectfully submitted that claim 34 which claims the process for recovering the full-length α_1 subunit of a T-type receptor meets the written description requirement. It also meets the utility requirement, since the product of the claimed process is useful and the utility of that product has been fully supported as described above.

CONCLUSION

The invention as now claimed is clearly useful and in compliance with the requirements for written description. Claims 28-33 describe an expression system for a defined class of nucleotide sequences which encode functional calcium ion channels of the low voltage activated T-type. These channels are clearly useful in screening for drugs that will be successful in treating epilepsy, heart conditions and a number of other conditions described above. The claim contains both structural and functional limitations. Claim 34 meets the written description requirement as set forth in *Amgen* and describes a useful invention since the product of the process has a known utility. Accordingly, it is respectfully submitted that claims 28-34 are in a position for allowance and passage of these claims to issue is respectfully requested.

Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

document to **Deposit Account No. 03-1952** referencing docket No. 381092000700. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: June 4, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

[Fig. 1 shows aligned amino acid sequences for the *C. elegans* C54D2.5 α_1 calcium channel subunit and initially identified portions of the calcium channel subunits of the invention.]

--Figures 1a and 1b show aligned amino acid sequences for the *C. elegans* C54D2.5 α_1 calcium channel subunit and initially identified portions of the calcium channel subunits of the invention.--

In the Claims:

28. (Amended) A DNA molecule which comprises an expression system for the production of a calcium ion channel [subunit] α_1 subunit protein which expression system comprises

a nucleotide sequence encoding a functional T-type, low voltage activated calcium channel α_1 subunit or the complement to said encoding nucleotide sequence, wherein said encoding nucleotide sequence comprises

(a) a nucleotide sequence encoding the amino acid sequence [set forth in] encoded by SEQ. ID. NO: 18 [or the complement of said nucleotide sequence]; or

(b) the complement of a nucleotide sequence that hybridizes under conditions of medium hybridization stringency to the nucleotide sequence of (a) [or the complement of said nucleotide sequence].

29. (Amended) The DNA molecule of claim 28 [which comprises a] wherein said encoding nucleotide sequence [that] encodes the [deduced] amino acid sequence [set forth in] encoded by SEQ. ID. NO: 18 [or its complement].

30. (Amended) The DNA molecule of claim 29 [which comprises the] wherein said encoding nucleotide sequence is that set forth in SEQ. ID. NO: 18 [or its complement].

31. (Amended) Recombinant host cells which are modified to contain the DNA molecule of any of claims 28-30.

32. (Amended) A method to produce a functional T-type calcium ion channel α_1 subunit protein which method comprises culturing the cells of claim 31 under conditions wherein said expression system produces said protein.

33. (Amended) A method to prepare cells which produce a functional T-type calcium ion channel α_1 subunit protein which method comprises introducing into said cells the DNA molecule of claim 28.